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EXAMINER	
SAUNDERS, DAVID A	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 720,371	Applicant(s) KALTOFT et al
	Examiner SAUNDERS	Group Art Unit 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 10/14/03.

☑ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 40, 60-88 is/are pending in the application.

Of the above claim(s) 80-83 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 40, 60-79, 84-88 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Amendment of 10/14/03 has been entered. Claims 40 and 60-88 are pending.

Claims 40, 60-79 and 84-88 are under examination. Method claims 80-83 are withdrawn since product claims are not patentable.

Claim 78 is objected to because of the following informalities: claim 78 is deemed intended to depend from claim 77, rather than cancelled claim 17. Appropriate correction is required.

Applicant's amendment has overcome the previously stated 112, 2nd paragraph rejections. The examiner concurs that the instant specification discloses the "Hayflich limit" as 23 PD.

Applicant's amendment has necessitated the following new 112 rejections:

Claims 60-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 60, "the initial cytotoxic T-cells" and "the tissue sample" lack antecedent basis.

In claim 61 "normal disease associated antigen activated cytotoxic T-cells" is unclear as to what is "normal", and what is "disease associated" about these cells. That is, it is not clear whether these are T-cells from a "normal" (healthy) individual or from a patient with a disease.

In claim 63 "functionally similar" is indefinite as to what the function intended may be. Is the function merely one of "promoting T-cell growth" (claims 61-62), or does

"function" also include the particular properties of promoting activation/differentiation associated with each listed cytokine?

In claim 69, "bone marrow" is an improper member of the Markush group of "body fluids." Bone marrow is a soft tissue, not a body fluid (see Cruse et al, page 39).

In claim 71 "having similar properties" is indefinite.

In claim 72 "functionally similar compounds" is indefinite; since the preceeding Markush Group recites compounds having diverse functions, it is not clear what common function, if any, these compounds, may have and thus what function a "functionally similar compound" must have.

Also note, the Markush group of claim 72 is improper by failing to recite -- the group consisting of -- after "selected from."

Claims 75-79 are unclear by reciting "an immunological composition" which has only antigen-activated cytotoxic T-cells as the constituent of the composition. Any composition must have two or more components (constituents) which make up the compositon. What component, besides the cells, is present?

Claims 75-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 75 recites new matter by virtue of reciting "immunological composition." The examiner cannot find this phrase in the

original disclosure. This phrase has less scope than more generically disclosed "pharmaceutical compositions" and has greater scope than more narrowly disclosed "vaccine compositions." Applicant is thus reciting a new subgenus of compositions.

Applicants' amendment/urgings has overcome the following prior art rejections of record.

1.) The 102 rejection over Liu et al (WO 88/07077); their method differs sufficiently from that instantly disclosed, that maintaining inherency would not hold.

2.) 102 rejection over Kaltoff et al (ref AV), who do not teach cytotoxic T-cells.

3.) The 102 rejection over Boel et al (5,877,017), since no details are given regarding the obtaining of the CTL clone 82/82, or the number of generations obtained thereof.

4.) The 102 rejection over Smith et al (2002/0034819). Even if one were to assume the 2000 fold expansion disclosed in para. [0031], the examiner concurs that the resulting overall expansion would represent less than 40 PD.

5.) The 103 rejection with Smith et al as a secondary reference. Since this reference has been considered not adequate for a 102 rejection, there is no point in using it as a secondary reference.

Claims 40, 60, 70-71, 73, 75-77 and 85-88 are rejected under 35 U.S.C. 102(e) as being anticipated by Riddell et al (5,827,642).

Applicant has traversed by arguing that Riddell et al disclose (col.9; lines 62-64) a value equivalent to ca. 30 PD, not 40 PD. This argument is unconvincing because

claim 40 merely requires that the cells claimed have an expected life span of 40 PD. There is no requirement that the cells have, in fact, expanded thus far.

Examiner maintains that one would have reasonably expected the T-cells of Riddell et al to have a life span of at least 40 PD. There is no teaching of Riddell et al that the exemplified expansion was the maximum achievable; as previously noted, Riddell et al used two factors (IL-2 and anti-cD3) which promote T-cell growth in culture. Two such factors is what applicant discloses as the minimum requirement to achieve 40 PD or unlimited growth –e.g. pages 3, 5, 10-12, especially the para; spanning pages 11-12. As applicant's disclosure is all encompassing, by virtue of broadly disclosing the mere use of two factors in culture to achieve the claimed degree of expansion, and as applicant's claims are not limited to any particularly taught combination of such factors, applicant's claims are open to rejection over any prior art showing culturing of T-cells with two such factors.

Further in support of examiner's position that the T-cells of Riddell et al would reasonably have an expected life span of 40 PD, note teachings that expanded cells can be arrested, remain viable, and then be stimulated to be further expanded. See, for example, col.13, lines 35-67; col. 22, line 44-col. 24, line 5. Also these teachings are consistent with instant claim 79.

Furthermore, the expansions taught by Riddell et al are not representative of the total degree of expansion (number of generations or population doublings) that the T-cells have undergone. Prior to subjecting T-cells to their taught "rapid expansion method" (REM), the cells have already undergone a number of divisions. That is, what

Riddell et al teach is a method that is to be conducted on an already established T-cell clone (col.9, lines 43+) which itself has previously been dividing (e.g. col.10, lines 45+). Thus all of applicant's calculations set forth in the traverse of the rejection do not reflect the actual number of divisions/doublings that the T-cells have undergone. One would, in fact, need to add to the number of clonal cell divisions (col.9, lines 62-64), which applicant calculates as 30 PD, the number of REM cell divisions (col.9 lines 38-40), which applicant calculates as 9-12 PD. The examiner thus calculates the total PD as 39-42.

Instant claim 70 is rejected, since cytotoxic T-cells are CD8+ (e.g. col.21, lines 41 and 64).

Regarding claims 71 and 73, Riddell et al teach (col.6, line 38) developing T-cells directed against antigens of tumor cells, which are of "neoplastic origin." Claim 71 is included because any cytotoxic T-cells directed against a tumor antigen would be a cell "having similar properties" to TILs.

Instant claim 75 is included since "immunological composition" does not distinguish over base claim 40. Further, any composition for "adoptive immunotherapy" (col.9, lines 54+) would be consistent.

Claims 76-77 are included because irradiated allogeneic fieder cells would provide allogeneic stimulation.

Claims 85-88 are rejected because there is nothing in the instant disclosure that any component, beyond the two factors which promote T-cell growth must be present in a culturing medium in order to achieve the recited PD values.

Claims 40, 60-73, 75-77 and 85-88 are rejected under 35 U.S.C. 103(b) as being anticipated over Haberman (5,188,959).

Applicant has traversed this rejection by merely arguing that Haberman shows less cellular expansion than do Riddell et al. This argument is unconvincing; since applicant's claims merely require that the cells claimed have an expected life span of 40 PD; the same rational applied by the examiner regarding Riddell et al applies to Haberman.

The examiner further notes, with respect to Haberman's teachings of using a combination of interlurkins, that a combination of IL-2 and IL-4 is an advantageous combination for culturing TILs from tumor samples (col.8, line 62-col.10, line 7). This is a preferred combination of lymphokines taught instantly (e.g. pages 11 and 75). Thus the examiner has reasonably stated anticipation.

Further, with respect to the continued proliferation of the T-cells of Haberman, note that he teaches activation of the T-cells with an activating agent, such as a lectin or an antibody to CD3 etc. in combination with the lymphokines (col.18, line 41-col.19, line 57). This teaching is consistent with the instantly recited presence of "one or more additional compounds" in claim 61 and with "functionally similar" in claim 71, which fails to identify the function.

From the above considerations, the examiner has included instant claims 40, 60-65, 71 and 85-88 in the stated rejection.

Regarding instant claims 66-67, note Haberman uses 1000 U/ml of IL-2 (e.g. col.18, line 15; col.21, line 22; col.22, line 11). Conversion to nM concentration would

involve factors depending upon manufactures and lot, but the examiner takes the following calculation as representative.

1 U IL-2/ml = 77 pg/ml = 77×10 (exp-12) g/ml (see Grooten et al, col.6, line 10).

Thus 1000 U IL-2/ml = 77×10 (exp-9) g/ml.

Converting to liters (L) one has 10 (exp-6) U IL-2/L = 77×10 (exp-6) g/L

Given that m.w. of IL-2 = 15.5 kD (Cruse et al) and converting to molar concentration one has

77×10 (exp-6) g/L over 15.5×10 (exp3) g/M equals 5×(exp-9) M/L, which converts to 5 nM. This is above the levels recited in claims 66-67.

Regarding instant claims 68-69, note Haberman at col. 17, line 40- col.18, line 40.

Instant claim 70 is included; note teachings of isolating CD8+ cytotoxic cells (e.g. col.16 line 58).

Instant claim 72 is rejected, because claim 61 has been rejected from teachings noted supra, and "functionally similar compounds" are taken to encompass anything within the noted teachings.

Regarding claim 73, tumor tissue (col.14, line 22; col.17, line 55) provides a source of T-cells from a tissue affected by a neoplastic disease.

Instant claim 75 is rejected because "immunological composition" does not define over the mere cells; however note, also, therapeutic uses of the disclosed T-cells (col.5, lines 62-66 and col.14, lines 16+).

Regarding claims 76-77, note Haberman teaches (col.21, line 62-col 22, line 14) the reactivation of the T-cells by a conventional T-cell activation method. These are shown at col.6, lines 57-col.7, line11. Irradiated lymphocytes from a second source animal are constituted of allo-antigens, in accord with the instant claims; note also reactivating with such cells as taught at col.23, lines 54+.

Applicant's urgings filed 10/14/03 have been considered but are not convincing.

Claims 40, 60-65, 68-73, 75-77 and 84-88 are rejected under 35 U.S.C. 102(e) as being anticipated by Flyer et al (6,316,257).

Flyer et al teach methodology similar to that of Riddell et al cited supra, in terms of rapidly expanding antigen specific T-cells; as noted supra regarding Riddell et al, the REM procedure is conducted upon T-cell lines or clones that have been previously established and that thus have already undergone numerous cell divisions. Flyer et al teach that such a cell line or clone will have typically undergone 10, 40 or 100 divisions/generations/populations doublings (col.14, lines 55+). This figure is that achieved prior to conducting the REM procedure. Various dependent claims are rejected following the natural set forth supra regarding Riddell et al.

Additionally, dependent claims 61-65 are rejected, since example 5 (col.28-29) shows culturing the T-cells with IL-2 and IL-4 (two cytokines) and anti-CD3 (OKT3 as an additional compound).

Claim 72 is included because anti-CD3 is taken to have the same function as the recited compounds, absent any recitation of what the common function of these compounds may be.

Regarding claims 68-69 note col.15, line 63-col.16, line 6.

Regarding claim 70, note col.23, lines 55+.

Regarding claims 71 and 73 note teaching of T-cells directed to tumor-antigens (col.13, line 6; col.15, line 32).

For claim 75 note col.7, lines 44+; with respect to claims 76-77 note teaching of restimulation with irradiated allogeneic cells—e.g. col.16, line 46-col.17, line 18.

Claims 40, 60 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riddell et al Haberman or Flyer et al, in view of Boel et al.

Riddell et al, Haberman and Flyer et al have been cited supra against claims 40, 60 and 73 regarding teachings of cytotoxic T-cells against cancer cells. Instant claim 74 merely recites a laundry list of well known cancers that are not specifically mentioned in the primary references; of these Boel et al teach melanoma as a well known cancer that is desirably treated with cytotoxic T-cells.

Claims 40, 75 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riddell et al, Haberman et al, or Flyer et al in view of Santoli et al (5,702,702).

The primary references have been cited supra against claims 40 and 75. Santoli et al show the further feature that it is known to obtain a cyotoxic T-cell line/clone, expand the cells in vitro with cytokines, and then irradiate the cells to prevent further cell division (e.g. col.3, line 58 col.4, line 7). This provides the advantage of preventing

adverse inflammatory conditions due to continued, in vivo proliferation of the T-cells; it hence would have been obvious to thus irradiate any of the T-cell lines/clones of the primary references prior to their in vivo administration.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00 am - 5:30 pm. The examiner can also be reached on alternative Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Saunders/tgd

February 11, 2004

David A Saunders

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